CURRENT LITERATURE

SEIZURE RISK WITH VACCINATION

The Risk of Seizures After Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine

Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Ward JI, Marcy SM, DeStefano F, Chen RT, Immanuel V, Pearson JA, Vadheim CM, Rebolledo V, Christakis D, Benson PJ, Lewis N

N Engl J Med 2001;345:656–661

BACKGROUND: The administration of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with adverse neurologic events, including seizures. We studied the relation between these vaccinations and the risk of a first seizure, subsequent seizures, and neurodevelopmental disability in children.
METHODS: This cohort study was conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures. We calculated the relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities.
RESULTS: Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42). Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). Neither vaccination was associated with an increased risk of nonfebrile seizures. Analyses of automated data alone gave results similar to the analyses of the data from medical-record reviews. The number of febrile seizures attributable to the administration of DTP and MMR vaccines was estimated to be 6 to 9 and 25 to 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities.
CONCLUSIONS: There are significantly elevated risks of febrile seizures on the day of receipt of DTP vaccine and 8 to 14 days after the receipt of MMR vaccine, but these risks do not appear to be associated with any long-term, adverse consequences.

COMMENTARY

Current childhood vaccines are, by all measurable standards, safe and effective. Relatively mild transient effects, however, can occur, and concern still exists about the possibility of more severe and longer lasting neurological disorders. Barlow et al.'s report provides the basis for assessing the absolute and relative increase in risk of febrile seizures as a function of time since vaccination. The study is particularly notable for its size (based on nearly 700,000 children under 6 years). They report that the risk of febrile seizures is increased almost sixfold on the day of diphtheria, tetanus, and pertussis (DTP) receipt and drops off to a negligible increase thereafter. For measles, mumps, and rubella (MMR), the effect is not seen until the 2nd week after receipt of the vaccine, where the risk is increased nearly threefold. They are also able to provide estimates of how many additional febrile seizures will occur as a result of vaccination with DTP (6 to 9 in 100,000) and MMR (25 to 34 in 100,000).

Their analysis of unprovoked seizures and other neurobehavioral disorders is focused on children who had febrile seizures. They found no difference between children whose febrile seizures were associated with MMR or DTP vaccinations compared with children whose febrile seizures occurred spontaneously. This lack of any association is reassuring; however, even in this enormous study, they were still not able to exclude sizeable effects (doubling or more) in the risk of epilepsy and other neurobehavioral outcomes. For this, it is necessary to read across the available, large, carefully conducted studies, all of which find no increased risk and of which, taken as a whole,

provide reasonable reassurance of MMR and DTP vaccines' safety (1–3).

The serious effects of the illness against which these vaccines protect are well documented and measurable. Encephalitis and resulting encephalopathies from many of the diseases themselves are prevented in as many children (perhaps more) as incur febrile seizures (a relatively benign outcome in the long run) following vaccination. Immunization for pertussis was terminated in Sweden in 1979. Over a 2-year period, over 2000 children were hospitalized with pertussis. Four percent suffered neurologic complications, and three died (4). A serious acute encephalitis caused by measles can occur in approximately 1 out of 1000 cases, and subacute sclerosing panencephalitis, a typically fatal complication of measles, occurs in approximately 1 in 1,000,000 cases. Such occurrences appear to be prevented through vaccination (5).

There will always remain some doubt about the "absolute" safety of childhood vaccines, specifically DTP (acellular or whole cell) and MMR. What Barlow et al.'s article and others help show is that any serious side-effects occur at an immeasurably small frequency, certainly smaller than the measurable effects of the illnesses they prevent. Changes in the vaccine formulation (e.g., whole cell to acellular) may also help to reduce side-effects, and further advances may help make current vaccines even safer.

by Anne T. Berg, Ph.D.

References

1. Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious neurological illness after immunization with diphtheria-tetanus-pertussis vaccine: A population-based case-control study. JAMA 1994;271:37–41.
2. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures after measles-mumps-rubella immunization. Pediatrics 1991;88:881–885.
3. Walker AM, Jick H, Perera DR, Knauss TA, Thompson RS. Neurologic events following diptheria-tetanus-pertussis immunization. Pediatrics 1988;81:345–349.
4. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J 1987;6: 364–371.
5. Subacute sclerosing panencephalitis surveillance: United States. MMWR Morb Mortal Wkly Rep 1982;31:585–588.